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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROBINSON, BINTA M	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/973,142	BIEDIGER ET AL.	
	Examiner	Art Unit	
	Binta M. Robinson	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-31 is/are pending in the application.

4a) Of the above claim(s) 1-6,8 and 15-31 is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 7, 9-14 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 6/3/01.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The restriction at paper no. 5 is modified such that the elected restricted group will include only claims 12-16 which which read on the elected species. Claims 1-11, 17-31, and the nonelected portions of claims 12-16 are withdrawn from examination as not reading on the elected subject mater. The examined group will consist of claims 12-16 drawn to the compound in claim 12 where R18 is aralkyl, B is as claimed, T is (CH2)b where b is 0, L is (CH2)n where n is 0, R4 is as claimed, R9 and R10 are as claimed, R23 is as claimed, g is 0 to 7, R6 and R7 are H, and Alk, B, R4, R6, R7, R9, R10, R18, and R23 are optionally substituted with at least one electron donating or electron withdrawing group. And the compound in claim 14 where , R18, R6, R7, R9, R10, B are as defined for claim 12 just above and R24,R25, R26, R27, and h are all defined as claimed, with the exception that R24 and R25 can not come together to form a ring, and B, R6, R7, R9, R10, R18, R24, R25, R26, and R27 are unsubstituted or substituted with at least one electron donating or electron withdrawing group.

Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not provide enablement for B, R1, R2, R3, R5, R6, R7, R9, R10, R11, R18, R24, R25, R26, and R27 being able to be substituted with all electron donating or electron withdrawing substituents; or R24 and R25 in claim 14 coming together to form any ring. There is also insufficient description of derivatives, esters, carbamates, aminals, amides, optical isomers or prodrugs of the compounds being claimed in claims 13 and 16; A derivative, ester, carbamate, aminal, amide, optical isomer or prodrug of the compounds depicted in claim 13 and 16 are not the same species as the compound depicted in claim 12. In the absence of how to make the ester, carbamate, aminal, amide, optical isomer or prodrugs of the compounds being claimed, there is no umbrella coverage springing forth from the claimed compound and the absence of examples of ester, carbamate, aminal, amide, optical isomer or prodrugs depicted in the specification. The applicant also does not disclose examples of any prodrugs in the specification which would be conventional formulations involving derivatization of functional groups that would be obvious. The lack of examples does not generate umbrella coverage for any prodrugs of the compounds depicted in claimed.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and

8. the level of the skill in the art.

The nature of the invention

The nature of the invention is the treatment of diseases in which the alpha 4 beta 1 integrin is involved with compounds as depicted in claims 12-16.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is regarding therapy for diseases mediated by alpha 4 beta 1 remains unpredictable. For example, many of the pathological states associated with alpha 4 beta 1 such as inflammation involve other pathways other than alpha 4 beta 1, such that the effect of inhibiting alpha 4 beta 1 on diseases is uncertain. For example, the drug natalizumab only had partial anti-inflammatory effects during a relatively short treatment period on patients with Chrohn's disease. (Andrian et. al., 348, 1, See Reference U) New England Journal of Medicine, page 70 Additionally, neutrophils can express alpha 4 beta 1 once they have migrated out of blood vessels, but it is questionable as to whether or not inhibition of alpha 4 integrins at this stage can interfere with leukocyte-mediated disease for example. See (Andrian et. al., 348, 1) New England Journal of Medicine, page 70. Chronic inhibition of alpha 4 integrins could also have unwanted effects. For example, in mice, an embryonic deficiency in the alpha 4 or beta 1 integrin chain is lethal before birth, suggesting that the use of pharmacological inhibitors of alpha 4 beta 1 integrin should be avoided during pregnancy.

The predictability or lack thereof in the art

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of alpha 4 beta 1-mediated diseases, whether the alpha 4 beta 1 was promoted or inhibited would affect the possible treatment of any disease.

Hence, in the absence of a showing of correlation between the diseases disclosed in on page 2 of the specification and the inhibition of alpha 4 beta 1, one of skill in the art is unable to fully predict possible results from the administration of the compound of claims 12-16 due to the unpredictability of the role of alpha 4 beta 1, i.e. whether promotion or inhibition would be beneficial for the treatment of the diseases.

The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The amount of direction or guidance present and the presence or absence of working examples

The instant specification does not disclose the inhibition action of these compounds in in vitro or in vivo experiments.

The breadth of the claims

The breadth of the claims is the treatment of diseases mediated by alpha 4 beta 1 integrin

The quantity of experimentation needed

The quantity of experimentation needed would be undue when faced with the lack of direction and guidance present in the instant specification and when faced with the unpredictability of this art.

The level of skill in the art

Even though the level of skill in the art is very high, based on the unpredictable nature of the intention and the state of the prior art and the extreme breadth of the claims and lack of guidance of these compounds effects on actual diseases or even on inhibition of alpha 4 beta 1 integrin, one skilled in the art could not use the claimed invention without undue experimentation.

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim(s) 13, 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 13 and 16 recite the limitation "derivative" in line 1 and the limitations, “esters”, “carbamates”, “aminals”, “amides”, “optical isomers” and “prodrugs” in line 2. There is insufficient antecedent basis for these limitations in the claim.

B. Claim 16 recites the limitation "derivative thereof selected from the group consisting of esters, carbamates, aminals, amides, optical isomers and prodrugs” in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein et. al. (US Patent 5521179) in view of Greene.

Bernstein et. al. teaches the compound intermediate as shown in Formula XIb, where, R is an acyl group of formula A.X.CO- in which A.X- taken together is RaOCONH- where Ra is hydrogen, R5 is hydrogen and R6 is the radical of formula B, Y- in which B is aryl or heteroaryl wich is pyrazinyl, which aryl. At column 132, see the compound intermediate and at columns 133 and 134, see the final product of compound of formula I where the radicals are defined for the intermediate. The difference between the prior art compound and the instantly claimed compounds is the teaching of an alkoxycarbonyl N-protected compound versus a benzyl protecting pyridinone compound. N-Benzyl

protecting groups and N-alkoxycarbonyl groups are standard protecting groups in the art. See pages 271 and 272 of Greene. It would have been obvious to one of ordinary skill in the art to substitute one standard N-protecting group, a N-benzyl protecting group, for another standard N-protecting group, the alkoxycarbonyl –N protecting group on the instant compound. Accordingly, the compounds are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the generic prior art compounds.

The IDS filed 6/3/01 has been considered.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph McKane, can be reached at (703) 308-4537.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone numbers are (703) 308-1235 and (703) 308-0196.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45AM to 4:45PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4242, (703) 305-3592, and (703) 305-3014.

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